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SYPHILIS AND THE LIVER.*

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Without doubt the most important fact elucidated by a study of the hepatic lesions of Syphilis is that, from an anatomical and histological point of view, no distinction can be drawn between secondary and tertiary syphilis.

Clinically I admit that such a distinction is useful, nor do I wish it to be thought for a moment that I imagine it can be done away with, although even clinically—as seen in connection with the syphilodermiæ—the establishment of a hard and fast demarcation between what is secondary and what tertiary leads not infrequently to confusion. The most that can be laid down is that when syphilis is acquired in the ordinary way, by sexual intercourse, the extension of the disease in general follows a definite course, the tissues tending to be affected in definite order. Or perhaps it is more correct to say that in syphilis as in other zymotic diseases—I use the term zymotic in its strict sense—there is a local or tissue predisposition, so that certain tissues are apt to be more extensively and more markedly affected than others, the virus multiplying more readily, so that in them as a consequence, there is an earlier and more pronounced reaction.

But while this is the case, the reaction in a given tissue is of like order, be the period of local infection early or late: at most there may be histological differences caused by variation in the interaction between virus and tissue. If the virus be strong or the tissue be possessed of feeble reactive powers, the histological appearances differ to a greater or less extent from what is seen when the virus is weak or the tissue possesses originally or has acquired strong reactive power. And as a corollary to this, it may be said that where the virus is powerful and there is rapid proliferation there, in such diseases as syphilis and tuberculosis, the course of the disease is modified so that we have to deal not solely or not in the main with the local disturbances caused by focal growth of the virus, but see well marked other anatomical changes brought about by diffusion of the toxins. In other words, where the tissues are susceptible and the virus relatively powerful there may be generalised tissue disturbances apart from the granulomatous developments directly caused by the focal proliferation of the germs. For at the start, it must be laid

* Being a contribution to the discussion upon Syphilis at the New York Academy of Medicine, March 9th, 1899.

down that although as yet we are uncertain as to the exact causative germ of the disease, syphilis is a disease of microbic origin. The more one studies, the more is one convinced that the analogy between tuberculosis and syphilis is complete—only in the one, we have isolated and studied the germ, in the other, we have not.

THE LESIONS OF CONGENITAL SYPHILIS.

For what do we find with regard to the hepatic manifestations of syphilis? Let us first take those of the congenital disease. There are many reasons why these should be considered first: (1) These were the first hepatic manifestations of the disease to be studied and clearly recognized; (2) they are much more frequent and more extensive than are hepatic lesions in the disease of post-natal acquirement, and (3) death occurring very frequently within a month or two after birth there is less uncertainty as to the period of development and duration of the lesions than there can be in the disease of adult life.

That the liver should be so frequently affected in this form of Syphilis is easily understood if we remember that the specific syphilitic lesions of the new born are congenital and not inherited, that the infection is through the placenta and that, as a consequence, the infected blood coming from the placenta passes through the liver before it reaches the heart or any of the other tissues of the foetal organism. Chiari's well known observation may here be repeated, namely, that in 144 cases of infantile syphilis, he found the liver affected, and that extensively, in 123, or nearly nine-tenths. In the adult on the other hand both brain and testicle are more frequently the seat of extensive lesions, and when it is remembered how relatively common is tertiary syphilis and how relatively uncommon specific disturbances of any one of these three organs, the contrast between the frequency of congenital and acquired hepatic disturbances becomes most manifest. At the same time I am not prepared to accept Fournier's statistics as perfectly reliable: careful observation of 3429 cases of tertiary syphilis would surely reveal clinical evidence of more than 9 cases of hepatic implication.

This is not the place for me to point out the vulgar fallacy of speaking of inherited instead of congenital syphilis—suffice it to say that Gärtner's *reductio ad absurdum* of the inheritance, so-called, of tuberculosis,* must hold equally for syphilis. Indeed, were it possible for the bacillus or germ of syphilis to be present in the ovum at the moment of fertilization, to lie latent during the embryonic period and only to cause reaction during foetal life, that is to say, after the different organs have assumed the form and structure which will pertain to them through

* Zeitschr. f. Hygiene, XIII., 1893, p. 101.

post-natal existence, even then, such presence of the germ would not be true inheritance: it would be an epiphenomenon; for true inheritance demands the carrying over of features peculiar to the germ plasm of the parents. The accidental inclusion of a microbe in the ovum is not a matter of inheritance.

The different lesions due to syphilis to be met with in the infant's liver are, I think, included in the following list:

I. Well-defined gummata.

II. Miliary gummata with generalised fibroid change affecting circumscribed areas of the liver.

III. Admixture of miliary gummata and generalised fibrosis affecting the whole organ, which is, in consequence, enlarged.

IV. Generalised atrophic cirrhosis without much evidence of gummata but associated with icterus, œdema, etc., the organ being very granular and contracted.*

Time forbids that I should quote examples of these different conditions. Quite the commonest is the second form in which there are no well developed gummata as generally understood, but on section through the affected areas, numerous minute focal collections of small round cells are to be made out, invisible or only just visible to the naked eye, and in their neighbourhood extensive pericellular fibrosis, so that the organ presents a patchy appearance, paler areas of large size standing out against the darker red or liver-colored background of the unaffected tissue. Here we have to deal with a relatively early and progressive stage of disease, in which there is little or no necrobiosis and development of gummy matter.

There are, however, fairly frequent cases on record of the development of true gummata, easily seen by the naked eye, some as large as an almond, and showing signs of contraction, recognised, not, I believe, in children born dead but in those dying as early as two weeks after birth (Canton.)†

The relationship between these miliary gummata and the gross gummata of the liver is that between miliary tubercles and isolated caseous tubercles of the same organ. We never think of suggesting that the two latter forms of tubercle indicate different periods of the tuberculous process. At most, we regard the first as of more acute, the second as of more chronic development. We know full well that miliary tuberculosis of the liver may develop at any stage of the disease, either soon after the primary infection or only as a terminal event after long years

* To this list I find must be added the (very rare) appearance of tumour-like masses, the result of centrifugal necrosis and fibroid change, with peripheral overgrowth of the liver tissue to which I refer later in discussing the syphilis of the adult.

† Trans. Path. Soc., Lond., XII., 1862, p. 113.

of slow and, it may be, intermittent extension of the disease elsewhere. The fact that both gross and miliary gummata may occur in the liver of the newly born is an absolute proof that the two forms are not characteristic of two different stages or periods of the disease. 'Absolute', that is to say, unless we are prepared to admit that while certain tissues such as the skin, present well marked secondary lesions, others may present either secondary or tertiary changes. Such an admission would make the terms 'secondary' and 'tertiary' valueless. For it must be kept clearly in mind that while the livers of these syphilitic infants show extensive fibrosis and indications which usually are recognised as of tertiary type, the cutaneous eruptions are secondary manifestations.

Over and above the granulomatous changes in the infant's liver it is most noticeable that a more generalised affection is peculiarly frequent, namely, fibrosis affecting either the whole organ or larger or smaller areas. Such fibrosis might be due to various causes; indeed, our knowledge of the etiology of cirrhotic changes in the liver, as in the kidney, and our knowledge of fibrosis in general is not sufficiently advanced to permit us to make positive statements. And, yet, since 1896 when, in this very room, although not before your Society, it was my privilege to deliver the Middleton-Goldsmith Lectures and I discussed the pathology of fibrosis in general, some little advance has been made in our conception of the process. For, on the one hand, Flexner* has shown that toxic substances (the blood serum of another animal), may lead to the development of cirrhosis, and, on the other, Weaver,† of Chicago, within the last few weeks, working (I think I may say) along lines suggested by certain publications of mine,‡ has demonstrated that bacteria exist which directly induce hepatic cirrhosis. Thus it would seem that whether in the process of excretion of toxic substances by the liver cells, or by the taking up of certain bacteria, and the influence of their toxins when so taken up, the liver cells may undergo a parenchymatous degeneration so intense that death ensues and, following thereupon, a replacement fibrosis occurs, more or less pure and unaccompanied by acute inflammatory change according as to whether the parenchymatous disturbance is unaccompanied by interstitial irritation or not. Where many miliary gummata are present, there eventually, much fibroid change is brought about by the tissue changes in their immediate neighbourhood.

We are not as yet in a position to state whether the fibroid change of this type in the liver of the syphilitic child is a consequence of the attempted removal of the syphilitic germs from the portal circulation by the agency of the endothelium of the hepatic blood vessels and by the liver cells, or whether it is the circulating toxins of the disease that

* Flexner, Trans. Path. Soc., Philadelphia, 1896.

† Weaver, Philadelphia Med. Jour., Feb. 4, 1899, p. 284.

‡ MONTREAL MEDICAL JOURNAL, July, 1898; British Med. Journal Oct. 22, 1898.

cause the disturbance. To me, it would seem that one or other of these causes must be at work. The pericellular character of the cirrhosis is against the change being in the main a fibrosis following upon rounded and miliary gummatous infiltration, while the fact that the change may affect the whole organ, as again the very extent of the areas affected when the whole organ is not involved, is quite opposed to the view that we have to deal with primary focal necroses such as are to be met with in Typhoid and other acute infective diseases, or with infarctous disturbance.*

If Marchand's cases of atrophic granular cirrhosis, occurring in fœtuses born dead are, as he holds, of syphilitic origin, they afford evidence of the extreme results of such fibrosis following upon generalised syphilitic parenchymatous hepatitis.

Thus, to sum up the broad features characterising the syphilitic manifestations in the infant's liver:—

(1.) Syphilis may lead either to granulomatous deposits in the organ or to interstitial fibroid changes.

(2.) The specific granulomata may be present either in the form of minute multiple miliary gummata, or of isolated larger gummata such as in general are regarded as being of tertiary nature.

(3.) It is not possible to regard the one form as secondary, the other as tertiary, for either may co-exist with cutaneous disturbances of the secondary type.

(4.) By analogy, the interstitial fibroid change, so common in infantile syphilis, would appear in the main to be secondary to a degeneration and necrosis of the hepatic parenchyma induced by the action of the toxins of the syphilitic virus upon the individual liver cells. In part it is developed in direct association with the development of miliary gummata.

THE LESIONS OF ACQUIRED SYPHILIS.

Passing now to the hepatic disturbances in syphilis, of post-natal acquirement, we find it more difficult to determine the age and duration of the lesions found, a difficulty due to the fact that syphilis is not in itself a cause of death during the months which immediately follow infection. I know of no adequate study upon the livers of those who, suffering from well marked secondary symptoms, have succumbed to intercurrent disease. A thorough investigation of the visceral changes occurring in the secondary period, remains as much a desideratum to-day as it was in the seventies when Jonathan Hutchinson called attention to this gap in our knowledge. It is however probable that in the vast majority of cases, the liver is not gravely affected during the secondary stages of the disease, for otherwise, it is most unlikely that with the vast number

* Dr. Jacobi informs me that he has met with one of these cases and could only conclude that it was of syphilitic origin.

of autopsies made annually, a fair number of instances of death during this stage, should not have been investigated, so that any marked departures from the normal in the condition of the organ, should by now have gained recognition. It is equally true, that there might be a certain amount of disturbance—the existence of miliary gummata or again a moderate extent of parenchymatous degeneration—which might easily escape detection, or be ascribed to other causes.

Some few cases are on record of extensive hepatic derangement during the secondary state. Thus, Hilton Fagge* reports the case of a female of 23 in whom there was a history of syphilitic rash with loss of hair and macular syphilides; jaundice supervened and the patient became drowsy and comatose. At the autopsy, the liver, which weighed 46 ounces, was of an opaque, bright yellow color and of dense consistence. The surface was mottled, the left lobe resembling very closely that of the infantile syphilitic liver;—on section, the organ appeared pale and semi-pellucid, and microscopically, the parenchyma was seen to be replaced by connective tissue. Unfortunately the description given does not extend to full details. But clearly here is a case of generalised cirrhotic change in secondary syphilis not unlike that found in the infantile disease.

There are on record some few other cases of like nature. To my regret during the last few months I have been away from laboratories and libraries, but in the course of an afternoon's search through the literature, I have come across quite a series of cases. One of the clearest examples is that recorded by Neumann,† in his admirable article upon syphilis, the case of a man of 20 years ill for about 8 months, who apparently was infected in June 1893 and in March 1898, a papular eruption was seen upon the external genitalia and mucosa of mouth together with slight icterus. The icterus increased and there was great abdominal pain, while ecchymoses appeared on various parts of the body. The liver diminished in size and 19 days later the patient died with uræmic appearances. The autopsy was performed by Kolisko who found a condition of catarrhal icterus with cholæmia together with the very interesting condition of "regeneration of the hepatic parenchyma in the form of adenomatous growths following upon acute atrophy. Kratz‡ records a similar case. Neumann quotes several cases of acute parenchymatous hepatitis in the secondary stage of the disease and holds it not improbable that there may be a relationship between the syphilis and acute atrophy of the organ.

Dittrich from a study of 46 cases has concluded that acute syphilitic hepatitis in general occurs during the secondary period. Engel-Rei-

* Hilton Fagge, *Trans. Path. Soc. London*, XVIII., 1867.

† Nothnagel's *Specielle Pathologie*, Vol. 23. p. 409.

‡ 66 *Versammlung d. Naturfor und Ärtze.*, Vienna, 1894.

mers,* on the other hand is inclined to believe that the acute yellow atrophy seen in recent syphilis is secondary to obstruction of the bile ducts, for in three cases he found enlarged glands compressing the ductus communis choledochus. I must, however, confess that it is difficult to follow his explanation; mere obstruction will not lead to acute yellow atrophy.

It will be noticed that in several of the above cases jaundice manifested itself. Now jaundice is a not uncommon event in secondary syphilis. Attention has frequently been called to its existence from the time of Ricord and Gubler onwards; Lancereaux alone collected twenty one cases, Lasch, † forty-nine. Within the last two years, Neumann, Joseph and Uhlmann have redirected attention to its prevalence. I cannot but think that this jaundice must afford another indication of what I have already dwelt upon in connection with infantile syphilis, namely, that the liver, being a great excretory organ, may in certain cases be so injured by the action of syphilitic toxins, that parenchymatous and it may be catarrhal hepatitis is set up and the jaundice be an indication of the functional disturbances due to this cause. This view appears to be more probable than either of the other suggested explanations, to wit, that the jaundice is obstructive and due either to specific growths in the bile ducts or to the pressure of enlarged lymph glands at the hilus of the liver upon the larger bile passages.

We thus, even in the early stages of the disease of postnatal acquirement, obtain evidence pointing to the existence of generalised effects of syphilis upon the liver. As I have pointed out elsewhere‡ a fairly extensive fibrosis, apparently independent of the gummatous developments, is not infrequently to be met with in cases where there is active progressive syphilis long years after primary infection.

Turning now to the more generally recognised evidence of syphilis affecting the liver in the tertiary stage, namely the gummata, and discussing first the large gummata, which are the most characteristic lesions of acquired syphilis, it must be clearly borne in mind that two distinct conditions are popularly confounded together and both regarded as tertiary manifestations, namely:—the fibroid pittings and cicatrices which are the final indications of gummatous deposits in the liver, which remain after complete absorption of the original gummatous mass. We not infrequently come across these disfigurements and distortions of the liver in the bodies of those who for years have presented no indications of active syphilis, and they must, I hold, be regarded as obsolete gummata. Indeed, in one case upon making microscopic sections through a

* Monatschrift f. prakt. Dermat., 1892, quoted by Neumann.

† Lasch, Berlin Klin. Wochenschr., 1894.

‡ MONTREAL MEDICAL JOURNAL, June, 1898, p. 401.

most characteristic puckering, I found scarce any fibroid tissue left : that also had undergone absorption. On the other hand,, we have to recognise gummata with cheesy or gummy contents surrounded by fibrous tissue, which are latent or obsolescent, and others again presenting like characters,—but surrounded by hepatic tissue which under the microscope presents infiltration with small round cells and evidence of progressive syphilis. It is these latent and active gummata which alone are of any importance, for both indicate that the disease, to say the least, has not been eradicated from the system.

The important point to notice is that in one liver we at times meet with all three forms above mentioned. I have come across cases at autopsy showing well marked cicatrices and puckerings of practically obsolete gummata, large well defined gummata with necrosed centres, and upon studying the sections of the liver from the neighbourhood of the latter, I have there seen the irregular minute collections of small round cells which in an infant's liver, we would have had no hesitation in describing as miliary gummata. These appearances I have seen in the liver of a man dying apparently only between two and three years after primary infection, as again in the liver of another infected 14 years before death.

The evidence before us all points to the fact that in the adult as in the infant's liver gummatous development may occur at any period after the disease has become generalised throughout the body.

From what has already been stated it follows that the same lesions are to be met with in the adult liver as are recognisable in the organ affected by ante-natal disease. There may be :

I. Large well formed gummata.

II. Miliary gummata.

III. Jaundice and acute parenchymatous hepatitis.

IV. Syphilitic cirrhosis.

But, clearly, the element of time introduces frequently a difference and appearance not seen in the infantile organ. Thus we encounter in addition:

V. Obsolescent gummata, large gummata undergoing involution and absorption with surrounding and limiting fibroid change and contracture. This is the lesion most frequently met with and most typical of the syphilitic liver of the adult* and,

VI. Obsolete gummata represented by puckering of the organ and a relatively small amount of fibroid growth radiating from the seat of the previous gummatous formation—and by nothing else.

* What is the causation of the coarse bands of fibrous tissue radiating from these obsolescent gummata, I must leave an open question. It has been suggested that they indicate a tendency for the fibroid change to be developed along the course of the main lymphatic vessels leading from the gummatous focus.

VII. A further lesion which must be referred to, one not seen in the infant* is the development of tumour-like outgrowths, so sharply defined and so large as not unfrequently to lead to the false diagnosis of malignancy. The structure of these masses affords some ground for believing them to be the outcome of a slow progressive centrifugal infection of the liver tissue from an original isolated gummatous focus (or small collection of neighbouring specific tubercles), with associated reactive hyperplasia of the liver tissue at the periphery—progressive infiltration of the newly formed liver tissue by miliary gummata and eventual replacement of these by fibrous connective tissue, so that, microscopically, these tumour-like out-growths present an outer layer of liver tissue infiltrated by collections of small cells, enclosing a dense mass of fibroid tissue with more or less evidence of 'gummy' degeneration.

Time, therefore, is an element causing difference in the appearance of the adult and infantile lesions. But this is not the only one. The other, and yet more distinctive, is the predominance of generalised fibrosis in congenital syphilis, of focal granulomatous changes in the syphilis of adults. The explanation of this difference would seem to be that the young liver cells are more susceptible and less resistant to the injuries inflicted by toxic substances. They are more prone to degenerate, and, if the view here enunciated be correct (namely that the fibrosis is largely of the 'replacement' type), we have in this feebleness of the young liver cells a sufficient explanation why fibrosis predominates. With the adult cell it is different. Inasmuch as a main function of the liver is to eliminate toxic substances from the circulating blood, its cells, with advancing life, become capable of withstanding toxins to a relatively very considerable extent. It is, indeed, remarkable to observe what extreme degenerative changes of the cloudy and even of the fatty type may be observed in the liver cells of an adult rabbit, for example, a few hours after intravenous inoculation of 1 ccm. of a culture of such a form as the colon bacillus, and yet in the course of a few days (as determined in other rabbits similarly treated), the liver cells may have completely recovered show no sign of the intense disturbance set up by flooding the system with the bacilli and their toxins.

Thus in the adult (as distinguished from the senile), there is not the tendency for extensive fibroid change to manifest itself under the action of irritants, which in the young, lead to the production of the same.

It may be asked why the liver in newly born infants more than other organs is susceptible to these degenerative changes. There are, it seems

* In this, as already stated, I am mistaken. I owe to Dr. Jacobi (verbal communication), a reference to a case by Cohn of one of these tumour-like formations in the infant presenting all the features here described, and Prévost (Ctes. Rendus de la Soc. de Biol., 1886-87, 4th series, III., p. 92), would seem to have encountered yet another case of his type.

to me, two main reasons : (1) the liver is especially concerned in the elimination of toxic substances and its cells bear the brunt of intoxication by the syphilitic virus. (2) Placed as it is, between the placenta and the general circulation of the foetus, its cells tend to eliminate toxic materials brought by the umbilical vein ; in this way, again, they bear the brunt of intoxication, and at the same time reduce the amount of toxic material capable of acting deleteriously on the other organs. But it must be remembered that other foetal organs may also show extensive fibroid change.

There is one other factor in the production of specific lesions which, so far, I have not touched upon, one which, judging from studies made more especially upon the syphilitic heart and brain, may very possibly be of signal importance. I refer to arterial change, endarteritis and periarteritis. We know however, practically nothing concerning the part played by this in hepatic lesions ; I can therefore, but mention it and pass it by.

Hence, to sum up; while the changes seen in the adult and infantile syphilitic livers are etiologically and anatomically identical, they tend to present differences due, in part, to their relative duration, in part to the reactive powers of the hepatic parenchyma at different life periods.

